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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/799,925 | 03/11/2004 | Glenn Kawasaki | NATH-003 | 6828 |

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| EXAMINER |
|---|
| SHIN, DANA H |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/799,925 | **Applicant(s)** KAWASAKI ET AL. | |
|---|---|---|---|
| | **Examiner** Dana Shin | **Art Unit** 1635 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 09 April 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/J. Schultz/

J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because:
Applicant's arguments filed on April 9, 2007 have been fully considered but they are not persuasive. Applicant argues that the quantification method taught by Hsuih et al. could not amplify small RNA molecules and any modified method of Hsuih et al. in view of Hannon would produce an "inoperable invention" by relying solely on Table 1. Applicant further contends that Wenz et al. do not teach detecting small RNA targets but teach amplification of cDNA via reverse transcription with target-specific probes.
As stated in the previous Office action mailed on January 8, 2007, both Hsuih et al. and Wenz et al. teach methods of quantifying the amount of target nucleic acid in a sample by contacting the sample with at least two oligonucleotides that adjacently hybridize to said target nucleic acid, whereby the resultant pseudotarget nucleic acid is amplified via PCR and quantified. As previously stated, neither Hsuih et al. nor Wenz et al. teach quantifying small RNAs such as siRNAs and shRNAs. However, this deficiency is cured by Hannon. Applicant further contends that Hsuih et al. do not suggest how their method can be used for small RNA targets, and therefore, the attempt to combine the method of Hsuih et al. with small RNA targets teaches away from the present disclosure and would result in an "inoperable invention" by showing Table 1 that discloses 20-mer probes. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Hannon's review article clearly teaches the genome-wide and therapeutic utility of siRNA/shRNA. For example, Hannon teaches that shRNAs will be useful for large scale loss-of-function genetic screens and RNAi-based therapeutics (page 250). Therefore, regardless of the length of probes of Hsuih et al. (Table 1), it would have been obvious to one of ordinary skill in the art to modify the quantifying methods of Hsuih et al. and Wenz et al. for siRNA or shRNA of Hannon, by replacing the long-stranded target nucleic acids of Hsuih et al. and Wenz et al. with the short, double-stranded target nucleic acids of Hannon. The skilled artisan would have been motivated to quantify the amount of siRNA/shRNA in a sample by modifying the methods of Hsuih et al. and Wenz et al. because siRNA/shRNA was a rapidly growing interest in the current state of the art for their potent inhibitory functions as of the priority date sought in the instant case as evidenced by Hannon, and therefore the skilled artisan would have been motivated to devise a method of detecting the amount of the newly emerged nucleic acid, siRNA/shRNA. Since target nucleic acid amplification via PCR had long been routinely practiced in the art as of the priority date sought in the instant case, the skilled artisan would have known how to optimize the PCR conditions with respect to the target sequence length. In conclusion, it would have been prima facie obvious to modify the teachings of the prior art to arrive at the method of quantifying an siRNA in a sample.

J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER